REMARKS

Reconsideration of the instant application in view of the above amendments and the following remarks is respectfully requested. Claims 2-16 are currently pending and under consideration. By the present amendment, claims 2-5, 11, and 12 are amended to more specifically recite particular aspects of the present invention. Support for these amendments may be found throughout the specification and claims as originally filed, and the amendments do not constitute addition of new matter. It should be noted that the above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related application.

Rejections Under 35 U.S.C. § 112

Claims 1-3, 15, and 16 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. More specifically, the Examiner asserts that the term "penumbral central nervous tissue" lacks support in the specification. Applicants note that claim 1 was canceled by the prior amendment submitted on April 2, 2007. Applicants, therefore, understand this rejection to apply to claims 2-4, 15, and 16.

Claims 5, and 11-14 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner asserts that the term "penumbral tissue" has no specific meaning, and requests that these claims are amended to clarify that the tissue referred to is adjacent to, or penumbral to the lesion.

Applicants respectfully submit that the phrase "penumbral central nervous tissue" is clearly support by the instant specification. For example, the instant specification describes transplanting bone marrow cells "into the penumbral tissue, adjacent to a lesion" (page 6, lines 21-24), and indicates that the lesion may be present in central nervous tissue, including brain

(page 2, lines 20-24). Thus, the instant specifically provides written description support for penumbral tissue that is central nervous tissue, *i.e.*, penumbral central nervous tissue.

In addition, the skilled artisan would understand the phrase "penumbral tissue" to mean tissue penumbral to a lesion or injury, in view of the common use of the term and the instant specification's description of penumbral tissue being adjacent to a lesion, and not within a lesion (page 6, lines 22-24).

Nonetheless, without acquicscence to this basis of rejection and in order to expedite prosecution of the instant application, the claims have been amended to more clearly recite that the cells are administered to tissue adjacent to the lesion. The term "penumbral" is removed from the claims. Applicants submit that the instant specification provides written description support for the tissue being adjacent to the lesion, and that the claims are definite. Therefore, in view of these amendments and remarks, Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection.

Rejection Under 35 U.S.C. §103

Claims 1-14 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Azizi *et al.* More specifically, the Examiner asserts that Azizi *et al.* describe the transplantation into the brain of human marrow stromal cells that survive, engraft, and migrate, and suggests that use of the transplant in the treatment of various central nervous system diseases. Although acknowledging that Azizi *et al.* only demonstrates transplant into healthy brain, the Examiner concludes that the mechanism of action of the implanted cells is an inherent property of the cells, so they would function in the same way regardless of the condition of the brain. The Examiner also concedes that Azizi *et al.* fails to teach that the transplanted cells would differentiate into parenchymal cells in the brain, but interprets the evidence presented in Azizi *et al.* to indicate that the transplanted cells become differentiated, since they are said to behave like endogenous CNS cells.

Applicants respectfully traverse this basis of rejection and submit that the claimed methods are not obvious over Azizi *et al.*, since this reference fails to teach or suggest each element of the presently claimed methods. Thus, the PTO has failed to establish a *prima facie* case of obviousness under 35 USC §103(a). (*See In re Mayne*, 104 F.3d 133, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (PTO has the burden of showing a *prima facie* case of obviousness.)). In order to establish a *prima facie* case of obviousness, the PTO must show: (1) that the cited reference(s) teaches or suggests all claim elements; (2) that the reference provides some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that according to the teachings of the reference, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. Various features of the claimed methods that are not taught or suggested by Azizi *et al.* are described below.

Azizi *et al.* fail to teach a method of activating the differentiation of endogenous neural cells by transplanting bone marrow cells into central nervous system tissue adjacent to injured or impaired neural cells. Instant claims 2, 4, 5, 6, and 7 (and claims 8-13 dependent therefrom) are directed to a methods of activating endogenous neural cells to differentiate into parenchymal cells, including neurons, comprising transplanting bone marrow cells into nervous tissue adjacent to impaired nervous tissue or cells. However, Azizi *et al.* do not describe methods for activating the differentiation of endogenous neural cells. Rather, it is only the instant specification that demonstrates that transplantation of bone marrow into ischemic brain activates endogenous brain stem cells to proliferate and to differentiate into parenchymal cells, including neurons (page 7, lines 21-25).

Furthermore, it can not be concluded that the methods utilized by Azizi *et al.* would inherently result in the activation of differentiation of endogenous neural cells. Azizi *et al.* do not specifically describe the transplantation of bone marrow stromal cells to an injured brain or spinal cord, and do not specify particular regions of tissue where cells are to be transplanted. As described in the instant specification, transplantation into tissue adjacent to an

injury or lesion, and not within the lesion, is an important feature of the claimed methods of the invention, since the adjacent tissue provides a receptive environment for the survival and differentiation of bone marrow (page 6, lines 22-25). In addition, the skilled artisan would appreciate that transplantation of bone marrow cells into a lesion or site of injury would most likely fail to induce differentiation of any endogenous cells, since the endogenous cells located at the site of injury or lesion are dead or impaired. Thus, Azizi *et al.* fail to teach important features of the presently claimed methods and, therefore, does not render the presently claimed methods obvious.

Applicants also note that the skilled artisan would not be motivated to modify the teachings of Azizi *et al.* regarding the transplantation of bone marrow stromal cells to promote differentiation of endogenous neural cells, to implant the bone marrow stromal cells at a site adjacent to a lesion or injury as presently claimed, absent the teachings of the instant specification with respect to the ability of the transplanted cells to activate differentiation of endogenous neural cells if implanted at a site adjacent to an injury or other lesion.

Azizi *et al.* fail to teach a method of treating injured brain or spinal cord comprising administering to a patient a composite of mesenchymal stem cells and neurospheres, as recited in instant claim 4. Instead, it is only the instant application that describes the use of a composite of mesenchymal stem cells and neurospheres. According to the instant specification, the composite of mesenchymal stem cells and neurospheres forms an axonal-dendritic like network, and cells derived from neural stem cells have a longer half span when present in the composite as compared to within the neurosphere alone (page 18, lines 20-23). In contrast, Azizi *et al.* only describe the independent administration of either mesenchymal stem cells or astrocyte precursors. *See, e.g.*, page 3911, column 2, lines 2-5, which state "Examination of sections stained with hemotoxylin and eosin indicated that there was no significant gliosis or infiltration of leukocytes round the implantation site of either the rat astroytes (not shown) or the human MSCs (Fig 3)." Thus, Azizi *et al.* clearly fail to teach each element of the method of claim 4 and doe not render this claim obvious.

Applicants further submit that Azizi *et al.* would fail to motivate the skilled artisan to modify its teachings to achieve the claimed method of implanting a composite comprising both mesenchymal stem cells and neurospheres, since Azizi *et al.* teach only the implantation of each separately and further demonstrates that the same results are achieved using either mesenchymal stem cells or astrocytes separately. For example, on page 3911, column 2, Azizi *et al.* state that both astrocytes and MSCs readily engrafted and migrated through layers of the brain. Clearly, the skilled artisan would not be motivated to administer a composite comprising both mesenchymal stem cells and neurospheres (or astrocytes), if the use of either one independently would be expected to achieve the same result as the combination.

In addition, Applicants further note that Azizi *et al.* fail to describe the use of neurospheres. Instead, Azizi *et al.* only describe the use of astrocytes obtained from adult rats. As described in Laywell, E.D. *et al.* (attached; *see*, abstract), astrocyte monolayers from the cerebral cortex, cerebellum, spinal cord, and SEZ can form neurospheres that give rise both to neurons and glia. However, the ability to form neurospheres is restricted to astrocyte monolayers derived during the first 2 postnatal wk, except for SEZ astrocytes, which retain this capacity in the mature forebrain. Laywell, E.D. *et al.* concluded that environmental factors, simulated by certain *in vitro* conditions, transiently confer NSC-like attributes on astrocytes during a critical period in CNS development. There is no indication in Azizi *et al.* that neurospheres were ever formed or used. Indeed, there is also indication in Azizi *et al.* that used therein were even capable of forming neurospheres. Thus, Azizi *et al.* fail to describe the use of a composite comprising neurospheres, and, accordingly, does not render the method of claim 4 obvious.

Azizi *et al.* fail to describe the administration of bone marrow stromal cells to central nervous tissue comprising an ischemic boundary zone, as recited in claim 6. While Azizi *et al.* makes general reference to transplantation of bone marrow stromal cells for the treatment of diseased and damaged nervous tissue, including Parkinson's disease, it does not specifically describe ischemic injury, such as that resulting from stroke. Furthermore, since Azizi *et al.* also fail to describe implanting bone marrow stromal cells to regions of tissue adjacent to a lesion or injury, it would not be apparent to the skilled artisan, based upon the limited teachings of Azizi

et al., to transplant bone marrow cells to an ischemic boundary zone. Thus, Azizi *et al.* fail to teach each element of this claim and does not render it obvious.

Finally, Azizi *et al.* fail to demonstrate that the implanted bone marrow stromal cells differentiate. Azizi *et al.* do not examine the implanted cells for expression of neural specific markers of differentiation. Rather, they merely demonstrate that the implanted bone marrow stromal cells show reduced expression of collagen and fibronectin following implantation. The skilled artisan will appreciate that this does not necessarily indicate that the bone marrow stromal cells have differentiated. Instead, it is more likely the effect of the cell no longer being grown on a tissue culture dish, which promotes adherence and expression of extracellular matrix proteins. In fact, Azizi *et al.* specifically state that fibronectin synthesis is frequently increased in cell culture. It is also very important to note that Azizi *et al.* do not claim that the implanted bone marrow cells differentiate. They state that the results demonstrate that human MSCs infused into rat brain can engraft, migrate, and survive, but they do not conclude that the cell differentiated. Thus, Azizi *et al.* do not describe methods of activating the differentiation of neural stem cells from implanted bone marrow stromal cells or endogenous central nervous system stem cells. Accordingly, the presently claimed methods, directed to activating differentiation of neural cells, cannot be considered obvious over Azizi *et al.*

The above discussion regarding Azizi *et al.*'s failure to demonstrate neural cell differentiation is of particular relevance to claims 2 and 3, which recite the differentiation of neural cells into neurons, specifically. Even assuming *arguendo* that Azizi *et al.* did demonstrate some resemblance of differentiation of the implanted bone marrow stromal cells, this reference provides no evidence that the implanted cells differentiated into neurons. Thus, this reference clearly does not render obvious the methods of claims 2 and 3.

In view of the above remarks and clarification with respect to the claimed methods, Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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